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An audit of topiramate use in a general neurology clinic

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The purpose of this study was to look at the efficacy and side effect profile of topiramate in a neurology unit. Using case notes, 94 patients who had been treated with topiramate were identified: 48 patients had taken part in clinical trials of topiramate, 46 received topiramate once licensed. Of these patients 24% had a greater than 50% decrease in seizure frequency. Patients with primary generalized epilepsy ($n = 12$) had a greater reduction in seizures compared with those with partial epilepsies ($n = 70$) $P > 0.03$. There was a high incidence (41%) of side effects, particularly psychiatric problems, leading to withdrawal of therapy in 41% of patients. Seven patients were admitted to hospital as a result of psychotic symptoms or depression. The incidence of psychotic symptoms (12%) was significantly higher for patients receiving topiramate compared with 191 patients attending the department on gabapentin (0.5%) and 270 patients attending the department on lamotrigine (0.7%) $P < 0.001$. 'Abnormal thinking', consisting of mental slowing and word-finding difficulties, occurred in 31%. The incidence could be significantly reduced by using 25 mg dose increments fortnightly as opposed to 100 mg weekly ($P > 0.03$). Although topiramate is an effective antiepileptic drug, its use is accompanied by a high incidence of particularly psychiatric side effects.

Key words: audit; topiramate; psychosis; epilepsy.

INTRODUCTION

Topiramate is a sulfanate-substituted monosaccharide[1] that is a very effective antiepileptic drug in clinical studies. The majority of randomized double-blind studies in patients with partial seizures have shown a greater than 50% reduction in seizures in between 35%[2] and 47%[3] of patients treated with topiramate. However, there has been a high incidence of adverse events leading to cessation of therapy in many patients.

An overview of double-blind randomized placebo-controlled studies has suggested that topiramate might be a very effective antiepileptic drug with an odds ratio of 50% responders of 4.22 (2.80–6.35). This was in association with a high dropout rate of 18% amongst 360 patients[4].

Topiramate has been licensed as an add-on therapy for the treatment of partial epilepsies since October 1995 in the UK. This retrospective study identified the patients who have been treated with topiramate in York prior to 1 January 1997 and looks at the effectiveness and the adverse effects of topiramate therapy in a general neurology outpatient clinic.

MATERIALS AND METHOD

All patients who had been treated with topiramate in York were identified by looking through the case notes of people attending the Department of Neurosciences, York District Hospital. All patients were under the care of a single consultant (P.M.C.). All patients were outpatients and living in the community. Ninety-four people were identified, 48 of whom had been in two international clinical trials with topiramate. The first study was an open label study of topiramate (TOP 107) as add-on therapy for drug-resistant epilepsy (36 patients), either partial or generalized. The second study was a double-blind placebo-controlled add-on study of topiramate (TOP 104) in patients with primary generalized epilepsy (12 patients), with an open label extension. The efficacy and side effect data were taken from the open-label extension study when all patients were receiving topiramate. The other 46 patients were treated with topiramate once it had received its UK licence. All 94 patients started treatment with topiramate at least 3 months treatment prior to January 1997. The majority of patients were keeping seizure diaries and efficacy data are derived from these. The side effects recorded are those spontaneously reported by the patient or a carer. Results have been analysed using Fisher's exact test, chi-squared test, Mantel Haenszel's chi-squared test and Student's t-test.

RESULTS

The patient demographic details are summarized in Table 1. The majority (765%) of the patients had the onset of epilepsy prior to the age of 18. Fourteen patients had

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Table 1: Patient demographics

Age (years)	Mean ± SD	36 ± 13
	Range	12–75
Men		49 (52%)
Women		45 (48%)
Age at onset epilepsy (years)	Mean ± SD	13 ± 12
	Range	0–58
Type of epilepsy	Localization-related	70 (74%)
	Primary generalized	16 (17%)
	Symptomatic generalized	8 (9%)

Table 2: Current antiepileptic drug therapy

		Mean dose ± SD	Dose range	
	n	(mg/day)	min^m	max^m
Carbamazepine	44 (47%)	993 ± 319	400	1600
Carbamazepine retard	12 (13%)	1200 ± 438	200	1600
Phenytoin	17 (18%)	355 ± 96	150	500
Sodium valproate	31 (33%)	1668 ± 605	500	3000
Vigabatrin	6 (6%)	2100 ± 490	500	3000
Lamotrigine	21 (23%)	250 ± 104	100	400
Gabapentin	12 (13%)	2010 ± 968	900	3600
Clobazam (regular dose)	10 (11%)	16 ± 10	10	40
Clobazam PRN	20 (22%)	10		
Clonazepam	2 (2%)	3.8 ± 0.75	3	4.5
Acetazolamide	2 (2%)	625	250	1000
Primidone	1 (1%)	250		
Tiagabine	1 (1%)	32		
Ethosuximide	1 (1%)	1000		
Remacemide	1 (1%)	800		
Diazepam	1 (1%)	10		

Table 3: New drugs tried prior to topiramate therapy

Drug	No. of patients
Vigabatrin	36 (39%)
Lamotrigine	63 (67%)
Gabapentin	40 (43%)
Remacemide	12 (13%)
Tiagabine	11 (12%)
Oxcarbazepine	1 (1%)
Losigamone	3 (3%)
Levetircetam	1 (1%)
Felbamate	1 (1%)

learning disabilities. All had seizure disorders resistant to current drug therapy and were having one or more seizures of any type per week. They had in the past tried between two and 14 antiepileptic drugs with a mean ±SD of 5.8 ± 2.0. Thirty-one (33%) were at the start of topiramate therapy on monotherapy, 36 (38%) on two antiepileptic drugs, 25 (27%) on three drugs and one (1%) on four drugs. Current drug treatment prior to topiramate therapy is summarized in Table 2. The majority (60%) of patients were taking carbamazepine, a third (33%) sodium valproate, 23% lamotrigine and 18% phenytoin. Only eight (9%) patients had not tried one of the new antiepileptic drugs (vigabatrin, lamotrigine or gabapentin) prior to topiramate therapy (Table 3).

Dosing schedule

The dosing schedule for topiramate differed throughout this study. In the initial open-label add-on study, patients were treated with a starting dose of 100 mg and weekly 100 mg increments. However, as this was accompanied by a high incidence of side effects, the dosage increments were reduced to a starting dose of 50 mg/day with 50 mg weekly increments. A 25 mg tablet became available in August 1996 and since then patients have been started on 25 mg/day and the dose increased every fortnight by 25 mg. Nineteen (20%) patients were started on 100 mg/day, 47 (50%) received 50 mg increments and 28 (30%) 25 mg increments. The dose was increased until either side effects appeared or seizure control improved. The mean dose achieved was 352 mg±216 mg/day. The doses obtained varied between 25 and 900 mg/day (Table 4). Patients remained on treatment from 3 days to 51 months. Overall there was over 102 patient man years of treatment with topiramate.

Efficacy

Twenty-two (24%) of patients treated with topiramate had a greater than 50% reduction in seizure frequency (Table 5). Three of these 22 patients were seizure-free for at least 3 months. Sixty-one (63%) patients were unchanged or worse as a result of topiramate therapy. One patient with myoclonic absence seizures and another with tonic–clonic seizures became seizure-free and are now driving. Patients with generalized epilepsies had a greater improvement in seizure frequency with eight (33%) having greater than 50% reduction in seizure frequency compared with those with partial seizures (14 patients (20%)) $P < 0.03$ (Mantel Haenszel chi-squared test). Patients with partial seizures who were in the open-label clinical trial currently show a greater but non-significant improvement with 11 (33%) patients having a greater than 50% reduction in seizures compared with three (8%) non-study patients who received topiramate since it was licensed (Table 6). This may be partly due to a lower mean dose and a shorter time on topiramate (NS) (Table 7).

Currently 45 (48%) patients are continuing on topiramate. Forty-nine (52%) patients have withdrawn from therapy, 24 (26%) for inefficacy and 39 (41%) due to side effects. Two female patients, both of whom had a greater than 50% reduction in seizure frequency, stopped topiramate therapy as they wished to become pregnant. One of them has subsequently restarted topiramate after the birth of her child, resulting again in a greater than 75% reduction in seizure frequency.

Table 4: Topiramate therapy

	All patients	Partial epilepsies	Symptomatic generalized	Primary generalized	
No. of patients	94	70	8	16	
Dose obtained (mg) ± SD	352 ± 216	343 ± 218	306 ± 256	398 ± 173	NS
range (mg/day)	25–900	25–900	25–700	25–600	
Length of treatment (mths) ± SD	13 ± 13	14 ± 14	6 ± 6	15 ± 10	NS
range (mths)	0.1–51.3	0.1–51.3	0.2–17	3–28	

Table 5: Efficacy of topiramate

	All patients	Partial epilepsies	Symptomatic generalized	Primary generalized
No. of patients	94	70	8	16
Seizure-free	3 (3%)	1 (1%)	0	2 (13%)
49–99% decrease	19 (21%)	13 (19%)	2 (25%)	4 (25%)
25–49% decrease	12 (13%)	8 (12%)	1 (13%)	3 (19%)
No change	53 (56%)	42 (52%)	4 (50%)	7 (44%)
Deterioration	7 (7%)	6 (9%)	1 (13%)	0

Patients with partial seizures vs. those with primary generalized epilepsies $P < 0.03$ (Mantel Haenszel chi-squared test).

Side effects

There was a high incidence of side effects leading to withdrawal of topiramate in 39 (41%) patients. The side effects encountered are summarized in Table 8. The commonest encountered side effects were psychiatric. Seven patients were admitted to hospital as a result of side effects from topiramate, six with psychotic symptoms and one with depression and anxiety. Eleven patients developed hallucinations and delusions, including severe psychoses in two patients, necessitating hospital admission and treatment with major tranquillisers. Two patients developed symptoms of depression and another three people had symptoms of depression and auditory and visual hallucinations. One of the patients who developed auditory and visual hallucinations on topiramate had previously had a similar problem when taking lamotrigine. Another patient, who needed a psychiatric referral because of severe depression and auditory hallucinations, had a diagnosis of Asperger's syndrome. A third patient, who developed visual and auditory hallucinations and depression whilst taking topiramate, has since gone on to develop a mild dementia secondary to cerebrovascular disease. The rest had no past history of significant psychiatric illness. The other psychiatric side effects were more minor and included anxiety, agitation and behavioural problems.

Another commonly reported side effects (31%) was 'abnormal thinking'. This consisted of mental slowing in association with word-finding difficulties. The incidence fell from 53% in those who had 100 mg increments weekly (19 patients), via 28% for those with 50 mg increments (47 patients) to 21% in those with fortnightly 25 mg increments (28 patients) $P < 0.03$ (chi-squared test). This has resulted in a reduction in the drop-out rate due to side effects from 47% to 36%.

Drowsiness (26%) was commonly reported, as was weight loss (18%). Paraesthesiae occurred in 8%. Speech disturbances were reported by 6% of patients. This consisted of difficulty in finding the correct words and was in association with slowing of cognitive function.

Renal problems are amongst the rare but well recognized side effects of topiramate. One patient had an episode of pyelonephritis and another renal colic secondary to renal calculi, subsequently demonstrated by ultrasound.

DISCUSSION

Topiramate undoubtedly is an effective antiepileptic drug with 23% of patients attending the outpatient clinic in this study having a decrease in seizure frequency by 50% or more. However, the results obtained in this study are much poorer than in the double-blind studies[2,4–6], reflecting the difficulty in treating and improving seizure control in the majority of people with continuing seizures attending neurology outpatient clinics. People entering clinical trials are highly selected and often unrepresentative of the population with drug-resistant epilepsy as many of the latter group have additional handicaps. In the double-blind studies in patients with partial seizures, between 35%[2] and 47%[3] had a greater than 50% reduction in seizure frequency. The majority of people in this report had the onset of their epilepsies in childhood and all patients had at least weekly seizures which had not responded adequately to currently available antiepileptic drugs. Such patients constitute a group with a poor prognosis for improvement in seizure control. All but eight patients had previously received one of the newly licensed

Table 6: Efficacy of topiramate in partial seizures: open-label study vs. non-study patients

	Partial epilepsies	Study patients	Non-study patients
No. of patients	70	33	37
Seizure-free	1 (1%)	1 (3%)	0
49–99% decrease	13 (19%)	10 (30%)	3 (8%)
25–49% decrease	8 (12%)	4 (12%)	4 (11%)
No change	42 (52%)	13 (41%)	29 (76%)
Deterioration	6 (9%)	5 (15%)	1 (3%)
No. continuing on topiramate	33 (48%)	12 (36%)	21 (57%)
Drop outs			
side effects	31 (45%)	16 (48%)	15 (41%)
inefficacy	21 (30%)	11 (33%)	10 (27%)

Table 7: Topiramate therapy in patients with partial seizures

	Partial epilepsies	Non-study patients	Study patients	
No. of patients	70	37	33	
Dose obtained (mg) ± SD	343 ± 218	301 ± 203	398 ± 224	NS
range (mg/day)	25–900	25–800	50–900	
Length of treatment (mths) ± SD	14 ± 14	6 ± 4	22 ± 17	
range (mths)	0.1–51	0.1–14	0.2–51	

Table 8: Side effects of topiramate

		Partial seizure patients	
	All patients	Study patients	Non-study patients
No. of patients	94	33	37
Total no. of side effects reported	249	117	60
mean per patient ± SD	4 ± 2.3	4.3 ± 2.2	3.0 ± 1.9
range	1–12	1–12	1–7
Commonly reported side effects			
Psychiatric problems	38 (41%)	14 (42%)	15 (41%)
Psychotic symptoms	11 (12%)	5 (15%)	4 (11%)
Depression	5 (5%)	2 (6%)	2 (5%)
'Abnormal thinking'	29 (31%)	14 (42%)	9 (24%)
Drowsiness	24 (26%)	10 (30%)	7 (19%)
Weight loss	17 (18%)	7 (21%)	5 (14%)
Poor memory	13 (14%)	8 (24%)	1 (3%)
Headaches	12 (13%)	5 (15%)	4 (11%)
Dizziness	9 (10%)	5 (15%)	1 (3%)
Parasthesiae	8 (9%)	4 (12%)	2 (5%)
Speech disturbance	8 (9%)	4 (12%)	2 (5%)
Insomnia	6 (6%)	1 (3%)	2 (5%)
Unsteadiness	6 (6%)	2 (6%)	4 (11%)
Renal problems	2 (2%)	2 (6%)	0
Double vision	3 (3%)	0	1 (3%)

drugs in the UK (vigabatrin, gabapentin or lamotrigine) or trial antiepileptic drugs. Patients with partial seizures who had not been entered into the open-label clinical trial had much poorer efficacy results (8% vs. 33%) than the study patients. This may in part be due to a lower mean dose and a shorter period on topiramate although this did not reach statistical significance.

Interestingly, although topiramate is currently only licensed as add-on therapy in patients with drug-resistant partial seizures, people with primary generalized epilepsies showed a significantly greater reduction in seizure frequency suggesting that topiramate may be a broad spectrum antiepileptic agent, effective for both partial and generalized epilepsies.

The most worrying aspect of topiramate has been its side effect profile, leading to withdrawal of the drug in 41% of patients. Seven (7%) patients were admitted to hospital because of probable drug-related side effects, six with psychotic symptoms and one with depression and anxiety. Hallucinations, either visual or auditory, occurred in 11 (12%) patients. A high incidence of psychosis of between 1.4%[7] and 8%[8] has been reported in people with epilepsy attending neurology outpatient clinics, particularly in those with partial seizures[9]. In an overview of the side effects of topiramate, a 3% incidence of psychosis and a 15% incidence of depression is reported[10]. However, in patients attending the neurology outpatient clinic in York, psychosis has been

a relatively rare occurrence in patients started on new antiepileptic drugs. No patients started on vigabatrin ($n = 88$) developed psychotic symptoms, one (0.5%) patient on gabapentin ($n = 191$) and two (0.8%) on lamotrigine ($n = 246$). No York patient has been admitted with drug-related side effects from these three drugs in the last 6 years.

Depression, agitation and behavioural problems were also common amongst patients treated with topiramate. Thirty-one percent of patients developed the problem of 'abnormal thinking' which consists of mental slowing and word-finding difficulties which seems to be a unique side effect of topiramate. Earlier articles on topiramate suggested that slower and smaller dosage increases might result in a lower incidence of this problem[3,6,10]. This study has added further evidence, with a significant reduction in this side effect using 25 mg increments fortnightly ($P < 0.03$). Interestingly, the incidence of psychiatric side effects was not altered by the slower dosing regime. The problem of 'abnormal thinking' has led to two patients being unable to continue in employment, despite improvements in seizure control.

This study confirms that topiramate is an effective antiepileptic drug. However, it does not need to be used with caution because of the high incidence of side effects.

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